ORIGINAL RESEARCH

Published in the specialty section: Sleep and Circadian Rhythms

Phase-Locked Auditory Stimulation During Slow-Wave Sleep Improves Overnight Memory Consolidation

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Received: 12 January 2026
Accepted: 18 June 2026
Published: 02 August 2026
Citation: Chen M, Okafor DN, Alvarez SR and Hartmann E (2026) Phase-locked auditory stimulation during slow-wave sleep improves overnight memory consolidation. *Front. Neurosci.* 20:1642087.
DOI: doi:10.3389/fnins.2026.1642087

Abstract

Background: Slow oscillations coordinate hippocampal–neocortical communication during non-rapid eye movement sleep. Closed-loop auditory stimulation can amplify these oscillations, but the behavioral benefit and the importance of stimulation phase remain uncertain.

Methods: We conducted a randomized, double-blind, within-participant crossover study in 36 healthy adults. Each participant completed adaptation, phase-locked stimulation, sham, and phase-jittered control nights. Brief pink-noise pulses were delivered during stable N3 sleep at the predicted positive half-wave of the frontal slow oscillation. Participants learned 120 semantically unrelated word pairs before sleep; delayed recall was tested the next morning. High-density electroencephalography quantified evoked slow-oscillation and spindle activity. Linear mixed-effects models included condition, night order, and presleep performance, with participant as a random intercept.

Results: Phase-locked stimulation increased slow-oscillation amplitude by 23.1% and fast-spindle power by 17.4% relative to sham. Overnight retention was 88.6% after phase-locked stimulation, 82.1% after sham, and 81.7% after phase-jittered stimulation. The phase-locked versus sham difference was 6.5 percentage points (95% CI 3.2–9.8; $p < 0.001$). Across participants, the stimulation-induced increase in slow-oscillation–spindle coupling predicted the memory benefit ($r = 0.46$, $p = 0.005$). Sleep architecture and morning vigilance did not differ by condition.

Conclusion: Precisely timed auditory stimulation strengthened endogenous slow-oscillation–spindle coordination and improved declarative memory without disrupting sleep. Phase specificity and coupling enhancement appear central to the behavioral effect.

Keywords: closed-loop stimulation; slow-wave sleep; declarative memory; electroencephalography; slow oscillation; sleep spindle; systems consolidation

1 Introduction

Sleep supports the stabilization and transformation of newly encoded memories. In the active systems consolidation framework, hippocampal representations are repeatedly reactivated during non-rapid eye movement (NREM) sleep and redistributed toward neocortical networks [1, 2]. This communication is organized by a hierarchy of rhythms: cortical slow oscillations below 1 Hz group thalamocortical sleep spindles, which in turn coordinate hippocampal sharp-wave ripples [3, 4]. Stronger temporal nesting among these events predicts better next-day memory [5].

The slow oscillation is a promising target for non-invasive intervention because it can be detected online from scalp electroencephalography (EEG). Auditory clicks delivered near its depolarizing up-state can enhance slow-wave activity and, in some studies, improve declarative memory [6, 7]. Yet outcomes vary considerably. Fixed stimulation schedules may drift from the endogenous oscillation, and control conditions often confound sound exposure with phase precision. It therefore remains unclear whether memory gains arise from phase-specific modulation or from non-specific sensory effects.

We tested whether closed-loop pink-noise pulses delivered at the predicted positive half-wave of the frontal slow oscillation would enhance overnight paired-associate retention. A phase-jittered condition used the same number and intensity of sounds but decorrelated them from the target phase. We hypothesized that phase-locked, but not phase-jittered, stimulation would (i) increase slow-oscillation amplitude, (ii) enhance fast-spindle activity and slow-oscillation–spindle coupling, and (iii) improve next-morning recall. We further predicted that individual coupling changes would explain variance in the behavioral response.

2 Materials and Methods

2.1 Participants

Forty healthy adults were recruited from the local community. Inclusion criteria were age 18–35 years, habitual sleep duration of 7–9 h, and regular bedtimes. Exclusion criteria included neurologic or psychiatric illness, diagnosed sleep disorder, psychoactive medication, shift work within 3 months, transmeridian travel within 4 weeks, and hearing thresholds above 25 dB HL at 0.5–4 kHz. Four participants withdrew before completing all experimental nights; the final sample comprised 36 adults (19 women; age 24.8 ± 4.1 years).

The Northbridge University Human Research Ethics Board approved the protocol (NU-HREB-2025-117). Participants provided written informed consent and received financial compensation. The study was preregistered before enrollment at the Open Science Framework (`https://osf.io/7n2cx`).

2.2 Design and Procedure

The randomized, double-blind, within-participant crossover protocol included one adaptation night followed by three experimental nights separated by at least 7 days. Condition order was computer-randomized in balanced blocks of six. The conditions were phase-locked stimulation, phase-jittered stimulation, and sham. Participants and morning assessors were blinded; an investigator not involved in testing configured the stimulation computer.

For 5 days before each visit, participants maintained a fixed sleep schedule within $\pm$30 min, verified by wrist actigraphy and sleep diary. Caffeine and alcohol were prohibited for 24 h. At 21:00, participants completed the psychomotor vigilance task and learned 120 unrelated noun pairs. Immediate cued recall continued until one pass through the list reached at least 60% correct.

Lights-off occurred at the participant's habitual bedtime. Delayed cued recall and vigilance were tested 45 min after awakening.

2.3 EEG Acquisition and Closed-Loop Stimulation

EEG was recorded from 64 active electrodes at 500 Hz, referenced online to FCz and re-referenced offline to linked mastoids. Impedances were maintained below 10 kΩ. Sleep was scored in 30-s epochs according to American Academy of Sleep Medicine criteria by two blinded raters.

The real-time detector used the average of F3 and F4, band-pass filtered at 0.25–1.25 Hz. Stimulation began after 5 continuous minutes of artifact-free N3 sleep. Following detection of a negative half-wave below -80 μV, an autoregressive predictor estimated the next positive peak. Two 50-ms pink-noise pulses separated by 1.075 s were presented binaurally at 45 dB above individual hearing threshold. Stimulation paused upon arousal, movement, or transition out of N3. The phase-jittered condition replayed the matched pulse count at delays sampled uniformly from 0.3–1.5 s after detection. During sham, triggers were recorded but no sound was delivered (Figure 1).

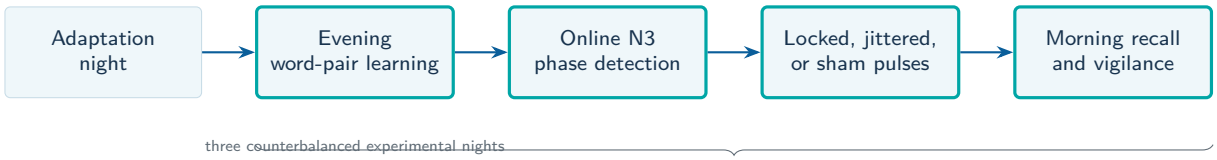

Figure 1: Study protocol. Each participant completed three counterbalanced experimental nights at least 7 days apart. Phase-locked and phase-jittered nights delivered identical acoustic energy; only pulse timing relative to the endogenous slow oscillation differed.

2.4 Memory, Vigilance, and EEG Outcomes

The primary behavioral outcome was overnight retention, defined as delayed correct recall divided by immediate correct recall and expressed as a percentage. The prespecified physiological outcomes were frontal slow-oscillation amplitude (0.5–1.0 Hz), fast-spindle power (12–15 Hz), and phase–amplitude coupling during the 2.5 s after each trigger. Coupling strength was quantified by the mean vector length of spindle-envelope amplitude over slow-oscillation phase. Analyses excluded trials with peak-to-peak amplitude above 500 μV or a scored arousal within 3 s.

2.5 Statistical Analysis

Analyses were performed in R 4.5.0. Linear mixed-effects models included condition, experimental-night order, and presleep performance as fixed effects and a participant random intercept. Planned contrasts compared phase-locked with sham and phase-jittered conditions; Holm correction controlled the familywise error rate. Pearson correlation tested the association between within-participant coupling change and retention benefit. Two-sided $p < 0.05$ indicated statistical significance. Model residuals were inspected for normality and homoscedasticity. Effect estimates are reported with 95% confidence intervals.

An a priori simulation indicated that 34 completers provided 90% power to detect a standardized within-participant effect of $d_z = 0.55$ at $\alpha = 0.05$. The analysis included every participant who completed all three conditions; no outcome values were imputed.

3 Results

3.1 Stimulation Was Phase-Specific and Did Not Alter Sleep Architecture

Participants received a median of 486 pulse pairs per stimulation night. In the phase-locked condition, the first pulse arrived at $18.2^\circ \pm 21.7^\circ$ relative to the predicted positive peak; phase-jittered pulses were approximately uniform across the oscillatory cycle. Total sleep time, sleep efficiency, N3 duration, wake after sleep onset, and morning vigilance did not differ among conditions (all Holm-adjusted $p > 0.20$; Table 1). No adverse events were reported.

Table 1: Sleep architecture and morning vigilance by experimental condition. Values are mean ± SD unless noted.

Measure	Sham	Phase-jittered	Phase-locked
Total sleep time (min)	421.3 ± 28.7	419.8 ± 30.1	422.6 ± 27.9
Sleep efficiency (%)	91.8 ± 3.7	91.3 ± 4.1	92.0 ± 3.5
N2 sleep (min)	209.5 ± 25.6	207.8 ± 27.2	208.9 ± 24.8
N3 sleep (min)	83.6 ± 15.2	82.9 ± 16.0	84.4 ± 15.7
REM sleep (min)	89.2 ± 14.9	89.8 ± 15.4	90.1 ± 15.1
Morning vigilance, median RT (ms)	244 ± 21	246 ± 23	243 ± 20

3.2 Phase-Locked Stimulation Enhanced Slow Oscillations and Spindles

Relative to sham triggers, phase-locked stimulation increased post-trigger slow-oscillation amplitude by 23.1% (95% CI 17.0–29.2; $p < 0.001$) and fast-spindle power by 17.4% (95% CI 10.5–24.3; $p < 0.001$). Phase-jittered stimulation produced smaller changes of 4.8% and 3.9%, respectively, neither of which survived correction. Coupling strength increased by 20.6% in the phase-locked condition compared with 2.7% in the phase-jittered condition (Figure 2). The induced spindle maximum occurred near the slow-oscillation positive peak, consistent with enhanced temporal nesting rather than a broadband auditory response.

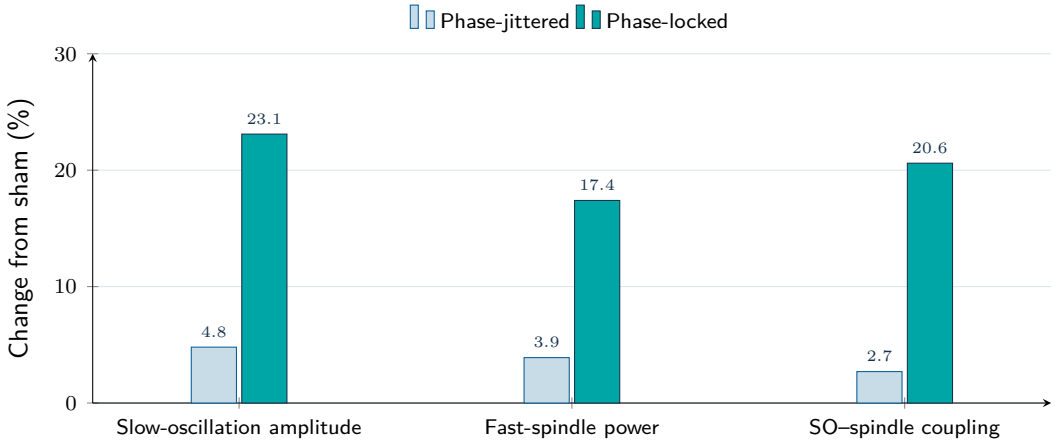

Figure 2: Physiological response to stimulation. Bars show condition estimates expressed as percentage change from sham. Phase-locked pulses enhanced slow-oscillation amplitude, fast-spindle power, and cross-frequency coupling; phase-jittered pulses did not produce reliable changes.

3.3 Phase-Locked Stimulation Improved Overnight Retention

Presleep recall did not differ among conditions ($p = 0.77$). Mean overnight retention was 88.6% after phase-locked stimulation, 82.1% after sham, and 81.7% after phase-jittered stimulation

(Figure 3). The adjusted phase-locked versus sham contrast was 6.5 percentage points (95% CI 3.2–9.8; $p < 0.001$; $d_z = 0.68$), and the phase-locked versus phase-jittered contrast was 6.9 points (95% CI 3.5–10.3; $p < 0.001$). Phase-jittered stimulation did not differ from sham (−0.4 points, 95% CI −2.8–2.0; $p = 0.74$).

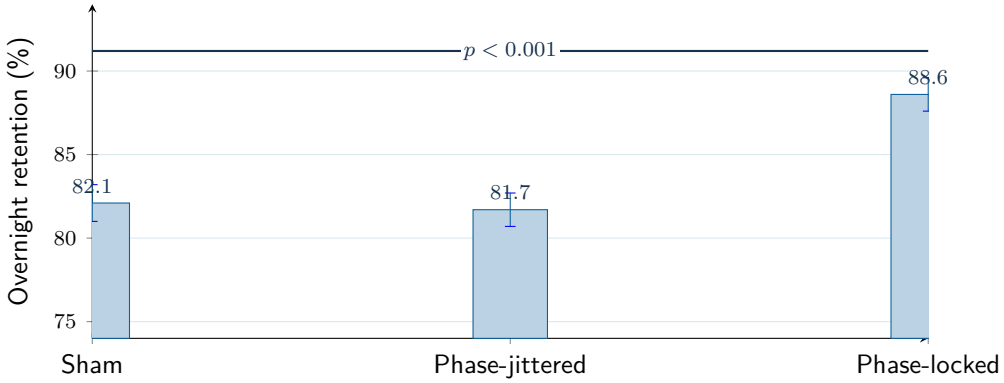

Figure 3: Overnight paired-associate retention. Bars show estimated marginal means ± SEM from the mixed-effects model. The y-axis is truncated to show the within-participant condition effect.

The within-participant increase in slow-oscillation–spindle coupling predicted the phase-locked retention benefit ($r = 0.46$, 95% CI 0.16–0.68; $p = 0.005$). Changes in total N3 duration did not predict retention ($r = 0.08$, $p = 0.64$), suggesting that temporal coordination, rather than additional deep sleep, accounted for the improvement.

4 Discussion

Precisely timed auditory stimulation during slow-wave sleep improved declarative memory and strengthened the physiological coordination thought to support systems consolidation. The same acoustic dose delivered at variable phases did not improve memory, despite preserving sleep architecture. This active control isolates phase alignment as a key ingredient of the intervention.

The 6.5-percentage-point retention benefit is consistent with reports that auditory up-state stimulation can enhance paired-associate memory [6]. Our physiological results extend those findings by linking the behavioral response to increased slow-oscillation–spindle coupling. Slow oscillations provide broad windows of cortical excitability, whereas spindles may protect and integrate hippocampal input [4]. The observed correlation supports this mechanistic account, although it does not establish mediation.

The absence of changes in sleep-stage duration or morning vigilance argues against a generalized arousal or sleep-depth explanation. The phase-jittered condition is particularly informative: participants heard comparable numbers of sounds, yet neither coupling nor retention increased. Closed-loop accuracy may therefore help explain heterogeneity in earlier stimulation studies [7].

Several limitations should be considered. The cohort was young and healthy, the study evaluated a single declarative task, and laboratory recordings covered only one night per condition. Scalp EEG cannot directly measure hippocampal ripples, so the proposed hippocampal–cortical mechanism remains indirect. The response also varied among individuals; anatomy, hearing sensitivity, and baseline coupling may influence effective timing. Future trials should evaluate multi-night dosing, adaptive phase models, older adults, and populations with impaired sleep-dependent memory.

In conclusion, phase-locked auditory stimulation amplified endogenous slow-oscillation–spindle coordination and produced a moderate improvement in overnight memory without measurable

sleep disruption. These results identify timing precision and cross-frequency coupling as practical targets for closed-loop sleep interventions.

5 Data Availability Statement

De-identified behavioral outcomes, derived EEG measures, the analysis script, and the preregistered protocol are available in the Open Science Framework repository at https://osf.io/7n2cx. Raw EEG data are available from the corresponding author under a data-use agreement because the high-density recordings may contain identifiable biometric information.

6 Ethics Statement

The study involving human participants was reviewed and approved by the Northbridge University Human Research Ethics Board (NU-HREB-2025-117). All participants provided written informed consent in accordance with the Declaration of Helsinki.

7 Author Contributions

MC: conceptualization, investigation, formal analysis, visualization, and writing—original draft. DNO: software, data curation, and investigation. SRA: methodology, signal processing, and writing—review and editing. EH: conceptualization, supervision, funding acquisition, and writing—review and editing. All authors approved the submitted version.

8 Funding

This work was supported by the Northbridge Brain Research Initiative (grant NBRI-25-041 to EH) and the Meridian Institute Neurotechnology Seed Fund (grant MINSF-2025-08 to SRA). The funders had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

9 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

10 Generative AI Statement

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12 Acknowledgments

The authors thank Lena Fischer for blinded sleep staging, the Northbridge Clinical Research Unit for participant coordination, and all study volunteers for their time.

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